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METHOD FOR MANUFACTURING 4-ACETYL TETRAHYDROPYRANE
[4-Asechirutetorahidoropiran no seiho]

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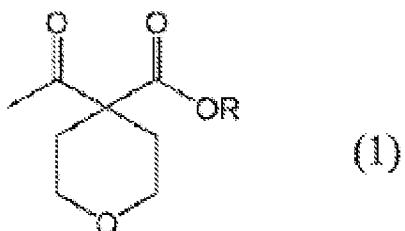
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[Claim(s)]

/2*

[Claim 1] A method for manufacturing 4-acetyl tetrahydropyrane characterized by reacting a 4-acetyl-4-alkoxycarbonyl tetrahydropyrane shown by the general formula (1) with hydrogen peroxide in the presence of a base.

[Formula 1]



(R denotes an alkyl group.)

[Detailed Description]

[0001]

[Technical Field of the Invention] The present invention relates to a method for manufacturing a 4-acetylalkoxycarbonyl tetrahydropyrane by decarboxylating a 4-acetyl-4-alkoxycarbonyl tetrahydropyrane. 4-acetyl tetrahydropyrane is a compound that is useful as an intermediate or raw material in the synthesis of pharmaceuticals.

[0002]

[Prior Art] A method in which 4-acetyl tetrahydropyrane was obtained by synthesizing ethyl 4-cyanotetrahydropyrane-4-carboxylate by reacting 2,2'-dicycloethyl ether and ethyl cyanoacetate,

* Claim and paragraph numbers correspond to those in the foreign text.

subsequently reacting this with potassium hydroxide to synthesize 4-cyanotetrahydropyrane-4-carboxylic acid, heating this at a high temperature to obtain 4-cyanotetrahydropyrane, and then reacting this with a Grignard's reagent was disclosed for a method for manufacturing 4-acetyl tetrahydropyrane (J. Am. Chem. Soc. 64 (1942):1672). However, this method was an industrially disadvantageous method of manufacture because a multistep reaction was required, a Grignard's reagent had to be used, the reaction operation and post-treatment were troublesome, and so forth.

[0003]

[Problems to be Solved by the Invention] An object of the present invention is to solve the above-mentioned problems, that is, provide a method for manufacturing 4-acetyl tetrahydropyrane capable of manufacturing 4-acetyl tetrahydropyrane from a 4-acetyl-4-alkoxycarbonyl tetrahydropyrane at a high yield and at mild conditions without requiring a troublesome operation.

[0004]

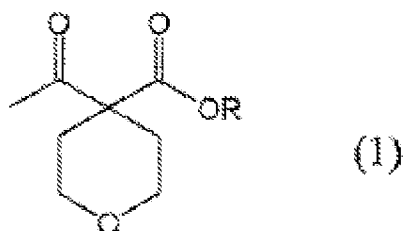
[Means for Solving the Problems] The object of the present invention is

[0006] solved in a method for manufacturing 4-acetyl tetrahydropyrane characterized by reacting hydrogen peroxide and a 4-acetyl-4-alkoxycarbonyl tetrahydropyrane shown by

[0004] general formula (1)

[0005]

[Formula 2]



(where R denotes an alkyl group.)

in the presence of a base.

[0007]

[Embodiments of the Invention] The 4-acteyl-4-alkoxycarbonyl tetrahydropyran used in the reaction of the present invention is shown by the aforesaid general formula (1). R in the general formula (1) thereof denotes an alkyl group.

[0008] An alkyl group having 1 to 5 carbons is especially preferable for the aforesaid alkyl group; a methyl group, ethyl group, propyl group (or an isomer thereof), butyl group (or an isomers thereof), and pentyl group (or an isomer thereof) are cited as examples therefor.

[0009] The base used in the present invention is an inorganic or organic base. An alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide; an alkali metal carbonic acid salt, such as sodium carbonate or potassium carbonate; an alkali metal phosphoric acid salt, such as sodium phosphate, disodium hydrogenphosphate, potassium phosphate or dipotassium hydrogenphosphate; an alkali metal organic acid salt, such as sodium acetate, potassium acetate, sodium

propionate or potassium propionate; and an alkali metal alkoxide, such as sodium methoxide or potassium methoxide, are cited therefor.

[0010] A tertiary amine, such as trimethyl amine, triethyl amine, ethyldiisopropyl amine, diethylisopropyl amine, triisopropyl amine, benzyldimethyl amine or benzyldiethyl amine; and a pyridine, such as pyridine, methyl pyridine or dimethyl pyridine, are cited for the aforesaid organic base. However, an amine, and more preferably, triethyl amine, is preferably used.

[0011] The amount of the aforesaid base used is preferably 0.1 to 5.0 and more preferably, 0.2 to 2.5 times the amount of moles of the 4-acetyl-4-alkoxycarbonyl tetrahydropyrane raw material. These bases may be used singly or by mixing two or more of them.

[0012] It is preferable that an aqueous solution of the hydrogen peroxide in the reaction of the present invention be an aqueous solution. The concentration thereof is preferably 5 to 70% by weight, and more preferably, 30 to 50% by weight. And the amount thereof used is preferably 0.1 to 3.0, and more preferably, 0.2 to 2.5 times the number of moles of the 4-acetyl-4-alkoxycarbonyl tetrahydropyrane raw material.

[0013] It is preferable to perform the reaction of the present invention in the presence of a solvent. The solvent thus used is not limited in particular as long as it can make the reaction system uniform. An alcohol, such as methanol, ethanol, isopropyl alcohol or t-butyl alcohol; and water are cited as examples therefor.

[0014] The amount of the aforesaid solvent used is preferably 0 to 50 mL, and more preferably, 0 to 30 mL/g of the 4-acetyl-4-alkoxycarbonyl tetrahydropyrane raw material. These solvents can be used singly or by mixing two or more of them.

[0015] The reaction of the present invention is performed in a method in which the 4-acetyl-4-alkoxycarbonyl tetrahydropyrane and hydrogen peroxide are preferable contacted in a liquid phase in the presence of the base. For example the 4-acetyl-4-alkoxycarbonyl tetrahydropyrane and the solvent are mixed in an inert gas atmosphere, and the hydrogen peroxide and base are subsequently added dropwise, heated, stirred, and so forth under normal pressure or under pressurization. The reaction temperature in that case is preferably 10 to 80°C, and more preferably, 30 to 50°C.

[0016] In addition, the resultant 4-acetyl tetrahydropyrane is separated and purified in a general method, such as column chromatography, distillation or recrystallization, after treating the hydrogen peroxide remaining after the reaction ends with a reducing agent.

[0017]

[Practical Examples] The present invention is specifically described next by citing practical examples, but the scope of the present invention is not limited thereto.

[0018] <Reference Example 1>

<Synthesis of 4-acetyl-4-methoxycarbonyl tetrahydropyrane>

This compound was synthesized in accordance with the method described in J. Chem. Soc. (1930):2525. 143 g (1.0 mol) of 2,2'-dicycloethyl ether, 276 g (2.0 mol) of anhydrous potassium carbonate, 10 g (0.06 mol) of potassium iodide, and 600 mL dimethyl formamide were added to a 1,000 mL (volume) glass flask provided with a dropping funnel, stirrer, thermometer and reflux condenser, and the temperature was raised to 80°C under stirring. Next, 139 g (1.2 mol) of methyl 3-oxobutanate were gradually added dropwise and this was allowed to react for 8 hours at the same temperature. After the reaction ended, 1,000 mL water were added to the reaction liquor and extracted three times with 600 mL ethyl acetate. Next, the organic layer was separated and subsequently dried with magnesium sulfate. After the filtering, this was vacuum distilled (85 to 95°C, 5 mmHg), and 95 g of 98% pure (percentage of surface area according to gas chromatography) 4-acetyl-4-methoxycarbonyl tetrahydropyrane were obtained as a light yellow liquid (50% yield). 4-acetyl-4-methoxycarbonyl tetrahydropyrane physical property values:

CI-MS(m/e) ; 187(M+1), ¹H-NMR(CDC l₃) ; 1.95 to 2.01 ppm(2H,m), 2.13 to 2.18 ppm(5H,m), 3.55 to 3.61 ppm(2H,m), and 3.73 to 3.79 ppm(5H,m).

[0019] <Practical Example 1>

202 g (1.03 mol) of 95% pure 4-acetyl-4-methoxycarbonyl tetrahydropyrane and 720 mL methanol were added to a 10 mL (volume) glass flask provided with a dropping funnel, stirrer, thermometer and reflux condenser, and the temperature was raised to 35°C under

stirring. Next, a liquid mixture of 201 g (2.06 mol) of 35% by weight hydrogen peroxide and 91 mL (0.73 mol) an aqueous 8N solution sodium hydroxide solution was gradually added dropwise. This was subsequently allowed to react for 5 hours after raising the temperature to 40°C. After the reaction ended, 100 mL of a saturated aqueous sodium sulfate solution were added to the resultant reaction liquor, the remaining hydrogen peroxide was treated, and the methanol was vacuum distilled. This was subsequently extracted three times with 500 mL of ethyl acetate, and the organic layer was separated next and subsequently vacuum distilled (113 to 115°C, 40 mmHg) to obtain 113 g of 99% pure (percentage of surface area according to gas chromatography) 4-acetyl tetrahydropyrane as a colorless liquid (yield: 85%). 4-acetyl tetrahydropyrane physical properties:

CI-MS(m/e) ; 129(M+1), ¹H-NMR(CDCl₃) ; 1.60 to 1.82 ppm (4H, m), 2.15 ppm (3H, s), 2.50 to 2.61 ppm (1H, m), 3.39 to 3.47 ppm (2H, m), and 3.96 to 4.02 ppm (2H, m).

[0020] <Practical Example 2>

0.39 g (2.0 mmol) of 95% pure 4-acetyl-4-methoxycarbonyl tetrahydropyrane and 5 mL methanol were added to a 10 mL (volume) glass flask provided with a dropping funnel, stirrer, thermometer, and reflux condenser, and the temperature was raised to 50°C under stirring. Next, a liquid mixture of 0.41 g (4.2 mmol) of 35% by weight hydrogen peroxide and 0.42 g (4.2 mmol) triethyl amine was gradually added dropwise. This was subsequently allowed to react for 2 hours at the same temperature. Upon analyzing the resultant

reaction liquor by high-speed liquid chromatography after the reaction ended, 0.26 g of 4-acetyl tetrahydropyrane was produced (100% yield).

[0021] <Practical Example 3>

0.38 g (2.0 mmol) of 99% pure 4-acetyl-4-methoxycarbonyl tetrahydropyrane and 0.39 g (4.0 mmol) of 35% by weight hydrogen peroxide were added to the same device in Practical Example 2, and the temperature was raised to 40°C under stirring. 0.25 mL (2.0 mol) of an aqueous 8N sodium hydroxide solution was gradually added dropwise. The temperature was subsequently raised to 50°C and this was allowed to react for 2 hours. Upon analyzing the resultant reaction liquor by high-speed liquid chromatography after the reaction ended, 0.21 g of 4-acetyl tetrahydropyrane was produced (80% yield).

[0022] <Practical Example 4>

0.40 g (2.1 mmol) of 99% pure 4-acetyl-4-methoxycarbonyl tetrahydropyrane and 5 mL methanol were added to the same device as in Practical Example 2, and the temperature was raised to 40°C under stirring. 0.41 mL (4.2 mmol) of a 35% by weight aqueous hydrogen peroxide solution and then 0.18 mL (1.4 mmol) of an aqueous 8N sodium hydroxide solution were gradually added dropwise. This was allowed to react for 5 hours at the same temperature. Upon analyzing the resultant reaction liquor by high-speed liquid chromatography after

the reaction ended, 0.27 g of 4-acetyl tetrahydropyrane was produced (100% yield).

[0023] <Practical Example 5>

Except for changing the base in Practical Example 4 to 0.18 mL (1.4 mmol) of an aqueous 8N potassium carbonate solution, the same reaction as in Practical Example 4 was performed. As a result, 0.27 g of 4-acetyl tetrahydropyrane was produced (100% yield).

[0024] <Practical Example 6>

Except for changing the base in Practical Example 4 to 0.50 mL (4.0 mmol) of an aqueous 8N sodium acetate solution, the same reaction as in Practical Example 4 was performed. As a result, 0.14 g of 4-acetyl tetrahydropyrane was produced (50% yield).

[0025] <Practical Example 7>

Except for changing the base in Practical Example 4 to 0.50 mL (4.0 mmol) of an aqueous 8N sodium hydrogenphosphate solution, the same reaction as in Practical Example 4 was performed. As a result, 0.24 g of 4-acetyl tetrahydropyrane was produced (89% yield).

[0026]

[Advantages of the Invention] According to the present invention, a method for manufacturing 4-acetyl tetrahydropyrane capable of manufacturing 4-acetyl tetrahydropyrane from a 4-acetyl-4-alkoxycarbonyl tetrahydropyrane at a high yield and at mild conditions without requiring a troublesome operation can be provided.